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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/478,748	06/07/95	WALDMANN	T 2026-4003US3

EXAMINER

HM12/0612

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ART UNIT	PAPER NUMBER
1644	29

DATE MAILED: 06/12/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/9/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 27 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 27 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☑ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Claims 1-26 have been canceled previously.
Claim 27 is pending and being acted upon presently.

2. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see form PTO-948 previously sent in Paper No. 7.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

3. The priority date of the instant claimed limitations appears to be that of the instant application (6/7/95).

4. In view of the Interview held on 3/9/00; the following New Grounds of Rejection are set forth herein.

As pointed out in the Interview; for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels.
It is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for in the claimed methods.

In contrast, it appears that applicant's arguments and the subject of the Waldmann declaration under 37 C.F.R. § 1.132 filed 3/26/99 (Paper No. 23) are drawn to the claimed methods as predetermining the three dosage/amount/soluble level determinations set for in the claimed methods prior to administering ^{90}Y-conjugated anti-Tac.

Also, it is noted that applicant's representative stated that neither she nor Waldmann were aware that the "mg" of ^{90}Y-conjugated anti-Tac were disclosed prior to applicant's priority date of 6/7/95, even though the administration of 5-15 mCi ^{90}Y-conjugated anti-Tac was disclosed in the prior art.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods as predetermining the three dosage/amount/soluble level determinations set for in the claimed methods prior to administering ^{90}Y-conjugated anti-Tac as it reads on treating leukemia/lymphoma as a disease associated with elevated levels of Tac-positive cells, does not reasonably provide enablement for methods of treating patients with any disease associated with elevated levels of Tac positive cells. For example, autoimmunity is associated with elevated levels of Tac positive cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims. Applicant has not provided sufficient and guidance nor objective evidence that the parameters set forth for treating patients with lymphoma and leukemia would be predictive for any patient with a disease associated with elevated levels of Tac positive cells. Patients with leukemia and lymphomas clearly differ in etiologies and pathologies as well as treatment methods from other patients with elevated Tac positive cells (e.g. patients with various autoimmune conditions). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without such guidance, setting forth the claimed parameters of administering ^{90}Y-conjugated anti-Tac to any patient with elevated levels of Tac-positive cells would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 27 is rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious Waldmann (Blood 82: 1701-1712, 1993; 892), as evidenced by Waldmann et al. (Blood 86: 4063-4075, 1995) AND/OR Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991).

The evidentiary references have been provided to support that the inherency of prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) encompasses the total amount of 2-20 mg anti-Tac encompassed by the claimed methods.

Waldmann et al. (Blood 86: 4063-4075, 1995) (see entire document, including the Introduction, particularly page 4064, column 1, and the Therapeutic Study Plan in the Materials and Methods) discloses that the Phase I trials disclosed in the Waldmann , Blood, 1993 teaching led to algorithm encompassed by the claimed methods. Therefore, given that the algorithm relied upon these Phase I studies; it would be inherent that the dosing set forth in the Phase I studies would meet the claimed dosage/amount/soluble level determinations.

Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) teach specific activities for Yttrium-90 labeled antibodies was 5-40 mCi per mg protein. Therefore, the prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody would meet the 2-20 mg anti-Tac encompassed by the claimed methods.

Waldmann et al. teaches treating patients with Yttrium-labeled anti-Tac antibody in the dosages ranges including the determination of soluble IL-2R levels, encompassed by the claimed methods (see entire document, including Materials and Methods such as the Therapeutic Study Plan, Results including Tables 1 and 2, Discussion). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced therapeutic modalities.

In the alternative, it would have obvious to give 20 mg of anti-Tac comprising 5-15 mCi Yttrium to patients with sIL-2R levels of greater than 50,000 given the clinical results/duration of the different patients in these studies. From the teachings of the reference, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments of record including the Waldmann declaration under 37 C.F.R. § 1.132 filed 3/2/99 (Paper No. 23) have been fully considered but are not found convincing in that Waldmann (Blood, 1993) appears to teach treating patients with Yttrium-labeled anti-Tac antibody in the dosages ranges including the determination of soluble IL-2R levels, encompassed by the claimed methods.

As pointed out in the Interview; for examination purposes given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels.

It is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for in the claimed methods.

Again, a species will anticipate a claim to a genus. See MPEP 2131.02.

Applicant's claimed methods recite various levels of ^{90}Y anti-Tac antibody based in patients having different sIL-2R levels. The prior art does not have to meet each asserted level, provided it meets one of the ranges of ^{90}Y anti-Tac antibody / sIL-2R levels.

In the Interview, applicant's focused on the lack of teaching that the prior art teachings of administering 5 - 15 mCi doses of ^{90}Y anti-Tac antibody (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) would encompass the total amount of 2-20 mg anti-Tac encompassed by the claimed methods; given that the rest of the Waldmann, Blood 1993 teaching was relying upon administering 20-50 mg of unlabeled anti-Tac antibody.

The evidentiary references Waldmann et al. (Blood 86: 4063-4075, 1995) AND/OR Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) have been provided to support that the inherency of prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody (see page 1711, column 1, paragraph 1 of Waldmann, Blood 1993) encompassed the total amount of 2-20 mg anti-Tac encompassed by the claimed methods in contrast to 20 - 50 mg of unlabeled antibody.

Applicant's arguments are not found persuasive.

10. Claim 27 is rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter.

As pointed out above; it appears that applicant's arguments and the subject of the Waldmann declaration under 37 C.F.R. § 1.132 filed 3/26/99 (Paper No. 23) are drawn to the claimed methods as predetermining the three dosage/amount/soluble level determinations set for in the claimed methods prior to administering ^{90}Y-conjugated anti-Tac.

For examination purposes in view of applicant's apparent interpretation of the claimed methods; Waldmann et al. (Blood 86: 4063-4075, 1995) presents an ambiguity with regard to inventorship.

The Therapeutic Study Plan (see page 4064, column 2) discloses that: "Based upon in vivo pharmacokinetic and bioavailability studies during the phase I trial; we (R.P.J., J.A.C., D.L.N., C.K.G. and T.A.W., unpublished observations) developed an algorithm to predict a dose of total anti-Tac (sum in milligrams or unlabeled and labeled antibody) that was sufficient to overcome the effect of soluble antigen levels (i.e. sIL-2Rα) . Based on this algorithm, the 9 patients in the phase II trial received a total quantity of anti-Tac in their initial treatment or pretreatment cycle that was determined by their soluble serum sIL-2Rα levels. Patients with a sIL-2Rα of less than 2,000 U/ml received a total dose of 2 mg of anti-Tac, those with 2,000 to 10,000 U/ml received 5 mg of anti-Tac and those with more than 10,000 U/ml received 10 mg of anti-Tac."

Therefore, Richard P. Junghans (R.P.J.); Jorge A. Carrasquillo (J.A.C.); David L. Nelson (D.L.N.); Carolyn K. Goldman (C.K.G.) are named developing the algorithm for the claimed methods; wherein only Thomas A. Waldmann (T.A.W.) Is listed as an inventor herein.

Because of this ambiguity, it is incumbent on applicant to provide a satisfactory showing which would lead to a reasonable conclusion that applicant alone is the inventor of the claimed invention. To resolve the ambiguity, applicant may file declarations by the non-applicant co-authors of the reference disclaiming the invention or a declaration by applicant setting forth the facts which provide an explanation as to why the non-applicant co-authors are not inventors.

11. Claim 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Waldmann (Blood 82: 1701-1712, 1993; 892) AND/OR Waldmann et al. (Important Adv. Oncol., 1994; 892) AND/OR Waldmann (Leukemia 7, Suppl 2 : S151-S156, 1993; 892) AND/OR Waldmann (Ann. Oncol. 5: 13-17, 1994; 1449) in view of Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) and Rubin et al. Ann. Int. Med. 113: 619 -627, 1990; 892).

The teachings of Waldmann (Blood 82: 1701-1712, 1993) AND/OR Waldmann et al. (Important Adv. Oncol., 1994; 892) AND/OR Waldmann (Leukemia 7, Suppl 2 : S151-S156, 1993; 892) AND/OR Waldmann (Ann. Oncol. 5: 13-17, 1994; 1449) are all of record. These references all teach the administration of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody to patients, resulting in either partial or complete remissions (see entire documents, including citations of record).

These Waldmann teachings differ from the claimed methods by not disclosing the particular mg amount of the 5 - 15 mCi doses of ^{90}Y anti-Tac antibody.

Vissendorf et al. (Int. J. Radiation Oncology 22:37-45, 1991) teach specific activities for Yttrium-90 labeled antibodies was 5-40 mCi per mg protein. Therefore, the prior art teaching of 5 - 15 mCi doses of ^{90}Y anti-Tac antibody would have been expected to meet the 2-20 mg anti-Tac encompassed by the claimed methods.

These Waldmann et al. references differ from the claimed methods by not disclosing the particular ranges of ^{90}Y anti-Tac antibody dosages as they would read on soluble IL-2R levels.

Waldmann (Blood 1993) clearly teaches that various types of ATL have circulating IL-2R/Tac encompassed by the claimed methods (See Table 1 on page 1703).

Similarly, the other Waldmann references teach elevated levels of the soluble IL-2R was associated with neoplastic disorders (e.g. page 132, column 2 to page 134, column of Waldmann, Important Advances in Oncology, 1994; page 14 of Waldmann Annals of Oncology, 1994).

In addition, Rubin et al. (Ann. Intern. Med., 1990) reviews that soluble Il-2 receptors were measured in a number of human diseases, including the malignancies encompassed by the claimed invention (see entire document, including page 621-622 and Table 1).

Therefore, the soluble IL-2 receptor levels encompassed by the claimed methods were expected levels of malignant patients at the time the invention was made.

Further, the Waldmann articles all disclose the association of IL-2 receptors and various diseases encompassed by the claimed invention as well as it was important to maintain the activity levels of anti-Tac antibody therapies in treating such diseases (see entire documents). The combined references of record also address the importance of pharmacokinetic analyses. Therefore, it would have been obvious to one of ordinary skill in the art to select for appropriate amounts of radiolabeled anti-Tac antibody (e.g. mg and mCi of anti-Tac antibodies) in vivo to achieve therapeutic efficacy in the face of soluble IL-2 receptors in patients. It would have been recognized that there would have been a range of therapeutic doses since differences in the nature of diseases as well as individual patients were known and expected in the art at the time the invention was made.

Again as pointed out above, it is not necessary that the prior art provide all of the dosages and amounts and ^{90}Y-conjugated anti-Tac to a patient with all of the soluble IL-2R levels; nor it is necessary for the prior art to predetermine the three dosage/amount/soluble level determinations set for in the claimed methods

For examination purposes, given the claimed recitation; all that is required of the prior art is to provide a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels.

Also, the combined references clearly taught efficacy of Yttrium-labeled anti-Tac antibody therapies including human patients and that a certain amount of mg of Yttrium-labeled antibody was associated with a certain activity (e.g. mCi) of said antibody;, therefore, it would have been expected that the ordinary artisan would have administered 5-15 mCi in total amounts of 2-20 mg to patients.

Also, given that the known advantage of radiolabeled antibodies over unlabeled antibodies at the time the invention was made was the ability to deliver a more effective means of delivering a therapeutic dose via the Yttrium label. Therefore, it would have been expected that Yttrium-labeled anti-Tac antibodies would require less than the 20-50 mg doses of unlabeled anti-Tac antibody in the treatment of diseases associated with Tac-positive cells (e.g. malignant cells).

Also, the prior art teaches the use of chimeric/humanized anti-Tac antibodies, which also would be expected to alleviate the HAMA responses to unlabeled murine anti-Tac antibodies and, in turn, would have been expected to require less than the 20-50 mg doses of unlabeled anti-Tac antibody in the treatment of diseases associated with Tac-positive cells (e.g. malignant cells).

This would have resulted in the effective dosages encompassed by the claimed limitations, including the amount of mg/mCi of anti-Tac as well as IL-2 receptor saturation levels at the time the invention was made.

As indicated of record, the references clearly teach the same amount or nearly the same amount of Yttrium labeled anti-Tac antibody for the same methods as presently claimed. Applicant has not provided sufficient objective evidence to distinguish between the amount of anti-Tac antibody taught or known by virtue of the combined references differs from that presently claimed. The claimed effective dosages are either taught by the references or it would have obvious to one of ordinary skill in the art at the time the invention was made that such amounts of mg/mCi of anti-Tac as well as IL-2 receptor levels would have been met by the administration of 5-15 mCi of Yttrium-labeled anti-Tac in patients having disease associated with elevated levels of Tac-positive cells.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to administer a dosage of mCi and an amount of ^{90}Y-conjugated anti-Tac to a patient with one of the soluble IL-2R levels encompassed by at least one of the three parameters encompassed by the claimed methods. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
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June 12, 2000